REMARKS

Applicants submit these remarks in response to the Office Action dated October 10, 2008. Claims 1-11 are cancelled, and claims 16-60 are withdrawn. Claims 62-68 are newly added, and do not add new matter. Claims 62-68 depend from previously presented claim 61. Claim 12 has been amended to depend from claim 61. Support for these amendments is discussed below. By these amendments, Applicants do not acquiesce to the propriety of the Office's rejections and does not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 USPQ.2d 1865 (US 1997). Applicants reserve the right to file continuing applications directed to the subject matter of any claim canceled or amended for any reason.

1-3. The Examiner stated that the submission filed on July 14, 2008 was entered, and the previous rejections have been withdrawn. New rejections and new grounds of rejection are presented in the current Office Action. October 10, 2008 Office Action ("OA"), page 2. These are addressed as follows in paragraphs corresponding to the numbering in the Office Action.

4-5. Claims 1-5, 7-15 and 61 are rejected under 35 U.S.C. § 112, second paragraph. Applicants respectfully disagree and request reconsideration and withdrawal of the rejection. Claims 1 and 2 have been cancelled, rendering the rejection of these claims moot. Claim 61 has been amended to clarify the terminology as it relates to SEQ ID NO: 1. Claims 14 and 15 have been amended to depend from claim 12 as kindly suggested by the Examiner.

6-7. Claims 1-5, 7-15 and 61 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully disagree and request reconsideration and withdrawal of the rejection. Claims 1-5 and 5-11 have been cancelled. Claim 12 now depends from claim 61, which recites a limited number of nucleic acid molecules, specifically, those encoding amino acid substitutions for wild type amino acids at up to five amino acid positions.

At least thirty five of these amino acid substitutions are provided in the specification. Table VI at page 71 provides the wild type amino acids for positions 159-161 and 168-169, as well as a selection of amino acid substitutions. One of ordinary skill can readily envision and write out the other possible substitutions, followed by testing as clearly described in Example 9 of the specification as filed.

The Examiner cites case law for the proposition that one cannot describe what one has not conceived (*Fiddes v. Baird*, 30 U.S.P.Q. 2d 1481 at 1483 (Bd. Pat. App. & Inter. 1993). In that case, claims to mammalian FGF's were found not to be patentable where only the bovine sequence was disclosed. The facts of the present situation are different. *Fiddes* presented a situation where the number of potential sequences was open-ended: the lengths of the other mammalian FGF's could differ, along with the polypeptide sequences. In contrast, the present Applicants have provided a finite number of sequences within the scope of the claims. The claimed sequences all use as a starting point SEQ ID NO:1. Variations are present at up to five specific amino acid positions. Because there is a limited number of amino acids and up to five positions with variation, the number of potential sequences is by definition *finite*, and capable of being written down without undue effort, thus meeting the written description requirement, in that one of skill in the art would recognize that Applicants were in possession of the claimed genus of claim 61.

8-9. Claims 1-5, 7-15 and 61 are rejected under 35 U.S.C. § 103 over Loeb (WO95/030007-A1, and Accession AAT05183) or Accession J03366, in view of the combined teachings of Black *et al.* J. Gen Virol. 77:1521-1527, 1996), Balasubramaniam *et al.*, J. Gen. Virol. 71:2979-2987 (1990), Brown *et al.*, Nat. Struct. Biol. 2:876-887, 1995), and Deonarian *et al.*, Gene Ther. 2:235-244, 1995). Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

With the cancellation of claims 1-5 and 7-11, and the amending of claim 12 to depend from claim 61, the issues have been narrowed. Although the Examiner states that Loeb teaches that *Herpesviridae* thymidine kinase comprises the DRH binding site, claims directed to this site, and to the Q substrate site, which is not taught by Loeb,

have been cancelled. The Examiner has not suggested that any of the references, either alone or in combination, disclose or teach amino acid substitutions at the specific positions recited in claims 61-68. Most of the references are cited for teaching the DRH binding site (Loeb, Balasubramaniam, Brown). Even more so, the combination of mutations at positions 159-161 *and* at 168-169 is not taught. Even given the general teaching of site-directed mutagenesis, there could be no expectation of successfully obtaining the combination of amino acid substitutions in the second generation of semi-random mutants as disclosed in Table VI and recited in claims 62-68.

The level of experimentation used to obtain the claimed sequences is illustrated by the following quote from the publication entitled *Herpes Simplex Virus-1 Thymidine Kinase Mutants Created by Semi-Random Sequence Mutagenesis Improve Prodrug-mediated Tumor Cell Killing*, Margaret E. Black *et al.*, Can. Res. 61:3022-3026 (2001):

> A semi-random mutagenesis approach was used to introduce combinations of amino acid substitutions within the HSV-1 TK active site. The possible codons for each semi-randomized codon are: L159, I or L; I160, L or F; F161, A, V, P, or L; A168, D, Y, V or F; and L169, F, Y, L, I, M, N, K, or stop. Because of codon usage, a number of undesired amino acids are also represented in the library, such as a stop codon at position 169. The total possible number of amino acid combinations is 512. **To ensure that all mutants were present multiple times, 12,376 clones were plated onto TK selection plates. A total of 1717 colonies were TK positive**, indicating that 13.9% of the 512 possible substitutions yielded detectable levels of enzyme activity.

(Emphasis added.) One of skill in the art could not predict from the cited references, either alone or in combination, which nucleotides to substitute to obtain the claimed sequences, where the actual experimentation entailed plating over twelve thousand clones to yield about one thousand seven hundred colonies. Furthermore, the cited references do not narrow the region to be mutated: the Applicants teach mutations to yield amino acid substitutions at one or more of positions 159-161 and 168-169. At best, the Examiner notes that Brown *et al.* teach a region consisting of residues 161-192, which is far broader than the five amino acid positions that are the focus of the present claims. Brown's region doesn't even include two of the five residues mutated according to the present claims: residues 159 and 160.

Applicants therefore request reconsideration and withdrawal of the rejection.

11. Claims 1-5, 7-15 and 61 are rejected on the ground of non-statutory obviousness-type double patenting over claims 1-31 of U.S. Patent No. 5,877,010 in view of the combined teachings of Black *et al.* J. Gen Virol. 77:1521-1527, 1996), Balasubramaniam *et al.*, J. Gen. Virol. 71:2979-2987 (1990), Brown *et al.*, Nat. Struct. Biol. 2:876-887, 1995), and Deonarian *et al.*, Gene Ther. 2:235-244, 1995), all as described in paragraphs 9-10 of the Office Action. Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

Claims 1-5 and 7-11 have been cancelled, and claim 12 now depends from claim 61. For the reasons discussed above in response to the rejection for obviousness under 35 U.S.C. § 103, it would not have been obvious to develop the specific mutated region claimed in claims 61-68. Even if, as the Examiner states, site-directed mutagenesis techniques are well-known, this does not mean that one would have an expectation of success. The Examiner pointed out that Brown *et al.* teach a much larger region encompassing that claimed, namely resides 161-192. If it took the plating and analysis of over twelve thousand clones to identify suitable mutations in the region defined by those five amino acids, there can be no expectation of successfully identifying those mutations starting with Brown's disclosure of an over thirty amino-acid region (positions 161-192). Furthermore, as noted above, Brown's region doesn't include two of the five residues mutated according to the present claims: residues 159 and 160.

CONCLUSION

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50,3207. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account.

Respectfully Submitted,

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